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| APPLICATION NO.                                                                                                                           | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-------------------------------------------------------------------------------------------------------------------------------------------|-------------|----------------------|---------------------|------------------|
| 10/761,571                                                                                                                                | 01/21/2004  | Swapan K. Ghosh      | 19026-14            | 3465             |
| 30565                                                                                                                                     | 7590        | 11/10/2004           | EXAMINER            |                  |
| WOODARD, EMHARDT, MORIARTY, MCNETT & HENRY LLP<br>BANK ONE CENTER/TOWER<br>111 MONUMENT CIRCLE, SUITE 3700<br>INDIANAPOLIS, IN 46204-5137 |             |                      | TONGUE, LAKIA J     |                  |
|                                                                                                                                           |             |                      | ART UNIT            | PAPER NUMBER     |
|                                                                                                                                           |             |                      | 1645                |                  |

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/761,571             | GHOSH, SWAPAN K.    |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Lakia J Tongue         | 1645                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 July 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16 and 27-53 is/are pending in the application.
- 4a) Of the above claim(s) 2,3 and 50-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-16 and 27-49 is/are rejected.
- 7) ☒ Claim(s) 10 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                                                   |                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                              | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

### **DETAILED ACTION**

Applicant has elected group I, Claims 1-16 and 27-29, drawn to a composition, classified in class 424, subclass 184.1. Claims 7-26 were canceled, claims 2, 3 and 50-53 were withdrawn and claims 1-16 and 27-49 are under examination as they relate to the elected species phytol derivative.

#### ***Information Disclosure Statement***

1. The information disclosure statement (IDS) submitted on April 26, 2004 has been considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

#### ***Specification***

2. The disclosure is objected to because of the following informalities: The second paragraph on page 6 of the disclosure has the word "or" duplicated. In addition, the final sentence of the second paragraph is lacking a period (Page 6, line 16). Lastly,

there are numerous page breaks within the disclosure beginning with page 1 following through to page 5.

Appropriate correction is required.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. New or novel should not be used in the title of an application.

The following title is suggested: Phytol derived immunoadjuvants and their use in vaccine formulations.

### ***Claim Objections***

3. Claim 10 is objected to because of the following informalities: the word "ganliosides" is spelled incorrectly. The correct spelling is gangliosides.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 1, 4-16, 27-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a composition comprising any vaccine antigen and a phytol derivative as an adjuvant and optionally a carrier. The claims are not limited to any specific antigen and thus include HIV antigens.

The specification lacks guidance and teaching to show that, for example, the composition comprising a phytol derivative as adjuvant and a vaccine antigen, e.g. HIV antigen, was generated or extracted and used to prevent infection (as would be expected from a "vaccine" antigen preparation).

The obstacles to vaccine development and therapeutic approaches with regard to retroviruses associated with AIDS in humans are well documented in the literature. These obstacles include: 1) the extensive genomic diversity associated with the HIV retrovirus, particularly with respect to the gene encoding the envelop protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to "hide" in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus, due to the blood-brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these

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obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen on its face. By definition vaccines must not only induce an immune response, but must be immunogenic to the extent that upon subsequent challenge with the live virus, development of the disease is prevented, or better yet infectivity does not occur. Fox (1994, BioTechnology 12:128) has reported on investigations reported by attendees at the First National Conference on Human Retroviruses and Related Infections and the frustrations encountered by several investigators. Those attending the conference have agreed that despite positive results coming from several laboratories, "AIDS researchers inevitably come back to the conference's central theme. No therapy had emerged as a sure winner in the campaign against HIV, not a preventive vaccine nor therapeutic vaccine nor any of the immune-system-boosting treatments." Thus it is clear that one would not accept claims to a vaccine or therapeutic against HIV on its face, absent evidence to the contrary.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). In the instant specification 1) insufficient direction or guidance is presented in the specification with respect to selecting other immunomodulators having the claimed functional feature of effectiveness in treating or preventing HIV infection, 2) there are no working examples which suggest the desired results of a vaccine antigen effective in treating or preventing HIV infection, 3) the nature of the invention involved the complex and incompletely understood area of

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immune correlates to HIV infection, 4) the state of the art shows that prior vaccines and treatment therapies have been largely ineffective for the intended purpose, 5) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level), and 6) the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by prior failures.

The claims also do not exclude a composition comprising a phytol derivative and a Plasmodium falciparum vaccine antigen. The obstacles to development of vaccines against malaria have also been well documented. Hodder, et al, 1996, investigated the disulfide bond structure of Plasmodium AMA-1 antigen and stated (page 29452) "We are currently producing the putative domains in an *E. coli* expression system...in an effort to establish which regions of the molecule are most relevant for the generation of protective immune responses."

It is apparent, from this report, that protective immune response to Plasmodium falciparum antigen are still in the investigation stage and that one skilled in the art would not readily accept claims to vaccines protecting against human malaria, absent evidence to the contrary, as being enabling.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988). In the instant specification there are no working examples which would suggest a vaccine against human malaria, the nature of the invention involves complex and incompletely understood areas of immunity to malaria, the state of the art shows that vaccines against human malaria are still in the

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developmental stage, the relative skill in the art is recognized as quite high (post-doctoral level) and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the lack of correlation between the generation of antibodies against malaria antigens and protection. Therefore, in view of all of the above, it is determined that it would require undue experimentation to make and use the claimed compositions comprising a vaccine antigen to protect against all type of disease including HIV and malaria caused by Plasmodium species.

Regarding claim 15, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.



The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1 and 6-11, 27-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart, Jr. et al (U.S. Patent 6,406,885 B1), in view of Takayuki Suga et al (Glycinoprenols: Novel polyprenols possessing a phytol residue from the leaves of soybean, J. Org. Chem., 1989, 54, 3390-3393).

Claims 1, 6-11, 27-49 are drawn to a composition comprising a vaccine preparation in unit dosage form including an effective amount of an antigen, an adjuvant component comprising a phytol, isophytol, or a phytol derivative and optionally a carrier.

Stewart, Jr. et al disclose engineered plants (soybean) expressing intimin antigen or the intimin fusion protein from *E. coli*. After the transformation of the soybean it is then fed to animals and/or humans to elicit the production of antibodies. Stewart, Jr. et al disclose that the antigens may <sup>be</sup> derive from but are not limited to bacteria, rickettsiae, fungi, viruses, parasites, drugs or chemicals. They may include small molecules such as peptides, oligosaccharides and toxins (column 23, lines 17-20). Additionally, in example XI Stewart Jr, et al discloses a gene gun-mediated transformation of various plants. Stewart Jr. et al disclose a method of transforming plants to express intimin or intimin fusion proteins. The plasmid is coated onto microparticles, <sup>with</sup> one gram of soybean

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embryos initiated from immature cotyledons and then are fed to animals, such as pigs (column 43, lines 15-37).

The composition inherently contains the phytol derivative because Suga et al. shows soybean comprising polyprenols in the structure found on page 3391, which is the same as the claimed structure in claim 6 of the instant application. Characteristics such as T-independent antigens, polypeptides and proteins are inherent in the composition of Stewart et al.

Claims 1, 9, 10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Franchini et al (Vitamin E as Adjuvant in Emulsified Vaccine for Chicks, Poultry Science, 1991, 70: 1709-1715).

Claims 1, 9, 10 and 13 are drawn to a composition comprising a vaccine preparation in unit dosage form including an effective amount of an antigen, an adjuvant component comprising a phytol, isophytol, or a phytol derivative and optionally a carrier wherein the antigen is selected from proteins, peptides, lipoproteins, glycoproteins, gangliosides, cerebroside, nucleoproteins, eukaryotic cellular isolates and prokaryotic cellular isolates.

Franchini et al verifies the effects on the immune response when light mineral oils in emulsified vaccines are prepared with inactivated bacteria and viruses. Franchini et al discloses different emulsified vaccines, each containing a strain of *Escherichia coli*. The vaccines differed in characteristics, some contained only light mineral oils, while others contained vitamin E (Page 1710).

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The instant specification defines phytol as a commercially available compound that is derived from Vitamin E or from chlorophyll as well as other naturally occurring species. In addition Stedman's Medical Dictionary defines phytol as an unsaturated primary alcohol derived from the hydrolysis of chlorophyll; a constituent of vitamins E and K<sub>1</sub>.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenk et al (U.S. Patent 5,030,453).

Claims 1 and 4 are drawn to a composition comprising a vaccine preparation in unit dosage form including an effective amount of an antigen, an adjuvant component comprising phytol, isophytol, or a phytol derivative and an optional carrier where the adjuvant component comprises phytanol.

Lenk et al discloses a substantially improved lipid vesicle that will include compounds such as nucleic acids, polynucleotides, antibacterial compounds, antiviral compounds, antifungal compounds, anti-parasitic compounds, tumoricidal compounds, proteins, toxins, enzymes, hormones, neurotransmitters, immunoglobulins, immunomodulators, dyes, radiolabels, radio-opaque compounds etc (column 12, lines 1-5). See figures 16 and 18-20.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Danilov et al (U.S. Patent 6,525,035 B1).

Claim 1 is drawn to a composition comprising a vaccine preparation in unit dosage form including an effective amount of an antigen, an adjuvant component comprising phytol, isophytol, or a phytol derivative and an optional carrier.

Danilov et al discloses a composition comprising a polyprenol, which is useful as an immunomodulatory agent. Danilov et al discloses tablets, troches, pills, capsules and the like that may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, flavoring agents such as peppermint, oil of wintergreen, or cherry. Various other materials may be present as coatings such as gelatin, wax, shellac or sugar and the like. Syrup may contain a sweetening agent, methyl and propylparabens as preservatives. Any material used in preparing the dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparation and devices. Lastly, the composition can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof in oils (column 6, lines 33-64).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ljt

  
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